

The endocannabinoid synapse

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The major psychoactive constituent of cannabis, delta⁹-tetrahydrocannabinol, affects pain, emotion and energy balance in humans and animal models by activating CB₁-type cannabinoid receptors in the brain and peripheral tissues. The two primary endogenous ligands of these receptors are the lipid-derived transmitters, anandamide and 2-arachidonoylglycerol (2-AG). Anandamide and 2-AG are non-redundant neural messengers, which are released upon demand and exert different biological effects in distinct regions of the mammalian brain. Significant progress has been recently made in understanding the structural and functional basis for 2-AG-mediated endocannabinoid signaling. Researchers have established some of the key molecular players involved in 2-AG formation and deactivation at excitatory synapses of the central nervous system, localized them to specific synaptic components, and showed that their assembly into a multi-molecular protein complex (termed the '2-AG signalosome') allows 2-AG to act as a retrograde messenger that bridges postsynaptic and presynaptic activity.